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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,940	02/26/2004	William D. Huse	66797-398	9547
25885	7590	01/17/2006	EXAMINER	
ELI LILLY & COMPANY PATENT DIVISION P.O. BOX 6288 INDIANAPOLIS, IN 46206-6288			HUYNH, PHUONG N	
		ART UNIT	PAPER NUMBER	
		1644		

DATE MAILED: 01/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/788,940	HUSE, WILLIAM D.	
	Examiner Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 18 November 2005.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 37-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 37-41 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

1. Claims 37-41 are pending.
2. Applicant's election without traverse of Group 4, claims 4-22 (now claims 37-41) drawn to a method for determining the therapeutic potency of a binding polypeptide, the binding polypeptide is a specific enzyme or functional fragment thereof, filed 11/18/05, is acknowledged.
3. Claims 37-41, drawn to a method for determining the therapeutic potency of a binding polypeptide, the binding polypeptide is a specific enzyme or functional fragment thereof, are being acted upon in this Office Action.
4. The disclosure is objected to because of the following informality: the "60/_____ " on page 1, line 4 should be filled in.
5. Applicant should amend the first line of the specification to update the relationship between the instant application and 10/001,202, filed 10/30/01, which claimed priority to provisional application 60/367,372 filed 10/30/00.
6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
7. Claims 37-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses only a method of synthesizing libraries of butyrylcholinesterase variants by codon-based mutagenesis wherein the butyrylcholinesterase enzyme is responsible for cocaine hydrolysis activity and expressing the butyrylcholinesterase variant libraries in mammalian cells (see pages 64-74 of the specification). The specification further discloses that the format of measuring association rates such as stopped flow kinetic

instruments, rapid quench flow instruments, surface plasmon resonance and evanescent wave instruments such as BIACore (See page 30-31 of the specification).

The specification fails to teach how measuring the association rate for binding (K_{on}) of *any* polypeptide to *any* ligand and comparing with association rate for binding polypeptide to an association rate for a therapeutic control *in vitro* is correlated with “improved therapeutic potency of any polypeptide” *in vivo*. There are no working examples in the specification as filed to demonstrate that an increase in association rate (K_{on}) for the binding polypeptide having at least about $8 \times 10^7 \text{ M}^{-1} \text{ S}^{-1}$ would be applicable to any receptor, any enzyme, any hormone, any immunoglobulin, any antibody, any humanized antibody, any human antibody, any integrin, any hormone receptor, any lectin, any membrane receptor, any transmitter receptor, any protease, any oxidoreductase, any kinase, and phosphatase, any DNA modifying enzyme, any transcription factor, any GTPase, any ATPase, any membrane channel, any growth factor, any insulin, any cytokine, any neural peptide, any extracellular matrix protein, any clotting factor and any functional fragments thereof. There is insufficient guidance with regard to the experimental reaction conditions such as buffer composition, temperature, coupling method, association time, flow rate that are crucial for one skill in the art to repeat the process to arrive at the claimed invention.

Sadir *et al* (J Biol Chem 273(18): 10919-25; May 1998, PTO 892) teach a method of determining the rate of association (K_{on}) of the binding polypeptide such as INF γ to the ligand such as the IFN γ receptor using BIACore and that the increase in the rate of association (K_{on}) can be caused by a number of factors such as the immediate rebinding of newly dissociated molecule at the surface of the sensor chip during the dissociation phase over time (See page 10922, column 2, first full paragraph, in particular) or progressive cleavage of the carboxyl terminus of binding polypeptide (See page 10924, column 1, Table II, second paragraph, in particular). Given that kinetic binding constant varies from one binding polypeptide to the next and an numerous undisclosed parameters, it is unpredictable whether determining K_{on} alone *in vitro* is sufficient to correlate with improved therapeutic potency *in vivo*.

For these reasons, it is not clear that the method of comparing the association rate (K_{on}) of the binding polypeptide to the control wherein the association rate (K_{on}) is increased will correlate with improved therapeutic potency for any binding polypeptide given many undisclosed parameters.

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8. Claims 37-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* method of optimizing the therapeutic potency of any parent polypeptide that binds to any particular ligand, any polypeptide such as any enzyme or functional fragment thereof, any enzyme such as butyrylcholinesterase or any functional fragment thereof as set forth in claims 37-41 wherein the progeny polypeptide exhibits a higher association such as at least $8 \times 10^7 \text{ M}^{-1} \text{ S}^{-1}$ that is associated with improve therapeutic potency.

The specification discloses only a method of synthesizing libraries of butyrylcholinesterase variants by codon-based mutagenesis wherein the butyrylcholinesterase enzyme is responsible for cocaine hydrolysis activity and expressing the butyrylcholinesterase variant libraries in mammalian cells (see pages 64-74 of the specification). The specification further discloses that the format of measuring association rates such as stopped flow kinetic instruments, rapid quench flow instruments, surface plasmon resonance and evanescent wave instruments such as BIACore (See page 30-31 of the specification). The specification defines the term "binding polypeptide" on page 5 as any polymer of amino acids that selectively associated with any ligand, any binding polypeptide can have at least 2, 5, 8, 10, 12, 15, 20, 25, 50, 100, 200, 400 or more amino acids...ranging from a couple to hundreds or even thousands of amino acids. The specification further defines a binding polypeptide can be any naturally occurring polypeptide such as any receptor, any enzyme, any hormone, such as any antibody, T cell receptor, integrin, hormone receptor, lectin, membrane receptor, transmitter (See paragraph bridging pages 5 and 6).

With the exception of the specific butyrylcholinesterase variants by codon-based mutagenesis for screening assays, there is inadequate written description about the structure associated with function of *any* binding polypeptide or any fragment thereof, let alone any functional fragment thereof comprising a K_{on} of at least $8 \times 10^7 \text{ M}^{-1} \text{ S}^{-1}$, for association with *any* ligand and having therapeutic potency. Even if the binding polypeptide is limited to butyrylcholinesterase, there is inadequate written about the association constant of *any* of said butyrylcholinesterase variants. Given the lack of a written description of *any* additional representative species of binding polypeptide or any fragment thereof having K_{on} of at least $8 \times$

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$10^7 \text{ M}^{-1} \text{ S}^{-1}$, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. Claims 37-41 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The " $8 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ " in Claim 37 represents a departure from the specification and the claims as originally filed.

It would be helpful if applicant points out the support for said phrase in the specification as filed.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,849,535 (Dec 1998, PTO 892) in view of US Pat 6,849,425 B1 (filed Oct 1999; PTO 892) and Lee *et al* (Transplantation 66(8): 1117-1119, 1998; PTO 892) or Jamieson *et al* (J Biol Chem 274(18): 12346-54, April 1999; PTO 892).

The '535 patent teaches a method of determining the therapeutic potency of a binding polypeptide such as hGH for either enhancing or inhibiting the growth hormone action in a patient (See column 3, lines 47-46, column 3, lines 57-59, column 4; lines 20-23, in particular). The reference method encompasses contacting the binding polypeptide such as hGH variant with the ligand such as the hGH receptor, measuring the association rate (K_{on}) of the binding polypeptide (hGH variant) to the receptor using BIACore instrumentation, comparing the

association rate of the hGH variant with the therapeutic control such as the wild type hGH, and the result shows that there is a difference in the relative association rate for the reference binding peptide (hGH variants) compared to the association rate of the therapeutic control (the wild type hGH) (See column 29 lines 15 bridging column 1-67, Table 1, in particular). The reference method further comprises changing one or more amino acids in the binding polypeptide and repeats the process indicated above for each and every hGH variant or mutant (See column 17, lines 66 bridging column 18, lines 1-8, Table 1, in particular). The reference association rate as indicated by K_{on} for the reference binding polypeptide hGH variant such as 852d increases by 4-fold relative to the wild type control (See column 51, 49-52, Table 9, in particular) and the increase correlates with improved therapeutic potency since the mutants show much larger improvements in the off-rate by 100 fold relative to the wild type (See column 51, lines 62-63, in particular).

The claimed invention as recited in claim 37 differs from the reference only by the recitation of said K_{on} is at least $8 \times 10^7 \text{ M}^{-1} \text{ S}^{-1}$.

The '425 patent teaches the higher the K_{on} value, the more efficacious of the molecules and this is because molecules with higher K_{on} values can specifically bind and inhibit their target at a faster rate (see col. 18, lines 3-12, in particular).

Lee *et al* teach a binding polypeptide such as IgM that has a association constant (K_{ass}) or K_{on} of $8.36 \times 10^7 \text{ M}^{-1} \text{ S}^{-1}$ and $4 \times 10^7 \text{ M}^{-1} \text{ S}^{-1}$, respectively, which is at least $8 \times 10^7 \text{ M}^{-1} \text{ S}^{-1}$ (See page 1119, column 2, Table 1, in particular).

Jamieson *et al* teach a binding polypeptide such as high mobility group domain protein HMG1domain that binds to cisplatin-modified DNA probe with an association constant K_{on} of 1.1×10^9 , which is at least $8 \times 10^7 \text{ M}^{-1} \text{ S}^{-1}$ (See page abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen binding polypeptide having an association rate constant (K_{on}) of at least $8 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ as taught by Lee *et al* or Jamieson *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Lee *et al* teach that high affinity and a high rate of association K_{on} are important and necessary for achieving a high rate of product formation but also for preventing side reactions such as inactivation (See page 10925, in particular). The '425 patent teaches the

higher the Kon value, the more efficacious of the molecules and this is because molecules with higher Kon values can specifically bind and inhibit their target at a faster rate (see col. 18, lines 3-12, in particular).

12. Claims 37 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,849,535 (Dec 1998, PTO 892) in view of in view of US Pat 6,849,425 B1 (filed Oct 1999; PTO 892) and Xie et al (Molecular Pharmacology 55: 83-91, 1999; PTO 892).

The teachings of the '535 patent have been discussed *supra*.

The claimed invention as recited in claim 40 differs from the reference only in that the method of optimizing the therapeutic potency of a polypeptide wherein the polypeptide is an enzyme.

The claimed invention as recited in claim 41 differs from the reference only in that the method of optimizing the therapeutic potency of a polypeptide wherein the polypeptide is an enzyme butyrylcholinesterase or a functional fragment thereof.

The '425 patent teaches the higher the Kon value, the more efficacious of the molecules and this is because molecules with higher Kon values can specifically bind and inhibit their target at a faster rate (see col. 18, lines 3-12, in particular).

Xie et al teach butyrylcholinesterase (BchE, EC 3.1.1.8) is a major detoxicating enzyme of cocaine (see page 83, col. 1, in particular) and certain mutation of human butyrylcholinesterase such as A328Y is four fold more efficient (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the polypeptide in the method of optimizing the therapeutic potency of any polypeptide by identifying the higher association rate having a rapid association rate constant (K_{on}) as taught by '535 patent and the '425 patent for the enzyme such as butyrylcholinesterase (BchE, EC 3.1.1.8) as taught by Xie et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Xie et al teach butyrylcholinesterase (BchE, EC 3.1.1.8) is a major detoxicating enzyme of cocaine (see page 83, col. 1, in particular) and certain mutation of human butyrylcholinesterase such as A328Y is four fold more efficient (see abstract, in particular). The '425 patent teaches the higher the Kon value, the more efficacious of the molecules and this is

because molecules with higher Kon values can specifically bind and inhibit their target at a faster rate (see col. 18, lines 3-12, in particular).

13. No claim is allowed.
14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.
15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
January 6, 2006

Christina Chan
CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600